

Patent No. 6,946,438  
Request for Cert. of Correction dated February 24, 2006  
Attorney Docket No. 0702-010411

02/806178

cgc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No. : 6,946,438 Confirmation No. 5455  
Inventors : Nagai et al.  
Issued : September 20, 2005  
Title : Use of Compounds That Reduce Alpha2-Antiplasmin  
In Vivo For The Preparation Of A Composition  
For The Treatment of Ischemic Stroke  
Examiner : Christopher James Nichola  
Customer No. : 28289



**Certificate**  
**MAR 06 2006**  
**of Correction**

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

ATTENTION: Decision and Certificate of Correction  
Branch of the Patent Issue Division

Sir:

In accordance with 35 U.S.C. §§254 and 255, we attach hereto Form PTO/SB/44 and a copy of proof of errors and request that a Certificate of Correction be issued in the above-identified patent. The following errors appear in the patent as printed:

- (1) Face of the patent, see Item (73) Assignees, second Assignee should read:  
-- Leuven Research & Development VZW --  
(This was incorrectly typed on the Issue Fee Transmittal as "VZQ".  
See correct name on Assignment document and Notice of Recordation.)
- (2) Face of the patent, see Item (56) References Cited, OTHER DOCUMENTS, second reference to Skolnick, line 3, "in th genomic era" should read  
-- in the genomic era --  
(See Form PTO-892, accompanying the Office Action mailed April 26, 2004.)
- (3) Face of the patent, see Item (56) References Cited, OTHER DOCUMENTS, page 2, Column 1, third reference to Nagai et al., line 3,  
"immunoneutralizt6ion reduce focal cerebral schemic" should read  
-- immunoneutralization reduce focal cerebral ischemic --  
(See Form PTO-892, accompanying the Office Action mailed May 5, 2003.)
- (4) Face of the patent, see Item (56) References Cited, OTHER DOCUMENTS, page 2, Column 2, last reference to Kopler, line 1, "Kopler, W.P. et al.  
"Adenovirus-mediated transfer of gene" should read  
-- **Kopfler**, W.P. et al. "Adenovirus-mediated transfer of a gene --  
(See IDS filed August 29, 2001, sheet 10 of 12 and page 1 of the Kopfler reference.)

03/02/2006 YPOLITE1 00000003 6946438

01 FC:1811

100.00 OP

{W0251457.1}

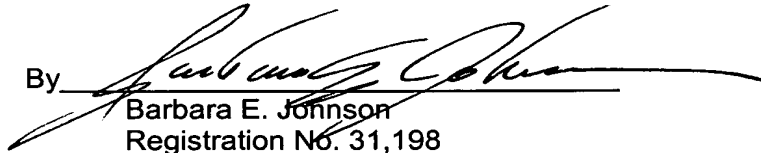
MAR 8 2006

Patent No. 6,946,438  
Request for Cert. of Correction dated February 24, 2006  
Attorney Docket No. 0702-010411

Error number (1) is an obvious typographical error made by Applicants. A check for \$100.00 is attached to cover the fee for correction of Applicants' mistake. The remaining errors are printing errors.

Respectfully submitted,  
THE WEBB LAW FIRM

By



Barbara E. Johnson  
Registration No. 31,198  
Attorney for Registrants  
700 Koppers Building  
436 Seventh Avenue  
Pittsburgh, PA 15219-1845  
Telephone: (412) 471-8815  
Facsimile: (412) 471-4094

MAR 8 2006

**UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION**

Page 1 of 1

PATENT NO. : 6,946,438  
APPLICATION NO. : 09/806,178  
ISSUE DATE : September 20, 2005  
INVENTORS : Nagai et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Face of the patent, see Item (73) Assignees, second Assignee should read:  
-- Leuven Research & Development VZW --

Face of the patent, see Item (56) References Cited, OTHER DOCUMENTS,  
second reference to Skolnick, line 3, "in th genomic era" should read  
-- in the genomic era --

Face of the patent, see Item (56) References Cited, OTHER DOCUMENTS, page 2,  
Column 1, third reference to Nagai et al., line 3,  
"immunoneutralizt6ion reduce focal cerebral schemic" should read  
-- immunoneutralization reduce focal cerebral ischemic --

Face of the patent, see Item (56) References Cited, OTHER DOCUMENTS,  
page 2, Column 2, last reference to Kopler, line 1, "Kopler, W.P. et al.  
"Adenovirus-mediated transfer of gene" should read  
-- **Kopfler**, W.P. et al. "Adenovirus-mediated transfer of a gene --

MAILING ADDRESS OF SENDER: The Webb Law Firm  
700 Koppers Building  
436 Seventh Avenue  
Pittsburgh, PA 15219-1845

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-2450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select Option 2.*

# Adenovirus-Mediated Transfer of a Gene Encoding Human Apolipoprotein A-I Into Normal Mice Increases Circulating High-Density Lipoprotein Cholesterol

William P. Kopfler, MD; Maureen Willard; Timothy Betz, MD; John E. Willard, MD; Robert D. Gerard, PhD; Robert S. Meidell, MD

**Background** In animal models of atherosclerosis, augmentation of circulating high-density lipoprotein (HDL) cholesterol exerts a protective effect against development of fatty streaks and promotes plaque regression.

**Methods and Results** To investigate the potential of gene transfer to increase HDL cholesterol, a fusion gene encoding human apolipoprotein A-I (apo A-I) under the control of the human cytomegalovirus (CMV) immediate-early promoter was packaged into a recombinant adenovirus (AdCMV apo A-I). BALB/c mice infected with AdCMV apo A-I by intravenous injection accumulate immunoreactive apo A-I in serum; levels 5 days after infection averaged 168 mg/dL. A 35% increase in HDL cholesterol and a 47% increase in total cholesterol were observed in mice infected with AdCMV apo

A-I compared with control viruses. Analysis of size-fractionated lipoproteins revealed that human apo A-I is incorporated into murine HDL particles. Expression of human apo A-I declined to <10% of maximum after 12 days and mRNA encoding apo A-I, prevalent 5 days after infection, was undetectable in the livers of infected mice after 12 days.

**Conclusions** We conclude that adenovirus-mediated transfer of a gene encoding apo A-I produces transient elevations of circulating HDL cholesterol of a magnitude correlated with important physiological effects. These observations suggest the potential for gene-based therapeutic strategies to reduce cardiovascular risk. (*Circulation*. 1994;90:1319-1327.)

**Key Words** • atherosclerosis • genes • viruses • lipoproteins • apolipoproteins

Epidemiological data demonstrate an inverse relation between circulating levels of high-density lipoprotein (HDL) cholesterol and the incidence of clinically significant atherosclerosis.<sup>1-4</sup> This relation holds for even small increments of HDL cholesterol, such that each 1-mg/dL increase in HDL cholesterol level is associated with a 2% to 3% decrement in cardiovascular risk.<sup>4</sup> Experimental evidence also supports a protective effect of HDL against atherosclerosis. Cholesterol-fed rabbits treated by infusion of purified homologous HDL are protected against the development of fatty plaques despite unchanged circulating HDL cholesterol levels.<sup>5-7</sup> This association between HDL cholesterol and the incidence of atherosclerotic vascular disease suggests that strategies to increase circulating HDL could have important clinical application. A modest increase in HDL cholesterol has been observed in patients treated with gemfibrozil,<sup>2</sup> an intervention associated with a reduced incidence of cardiac events. Trials intended to specifically assess the effects

of intervention to increase HDL cholesterol on the development and progression of atherosclerosis are in progress.<sup>8,9</sup>

HDL appears to exert its antiatherogenic effect by mediating reverse cholesterol transport, in which cholesterol is mobilized from peripheral tissues and transported to the liver.<sup>10-12</sup> The small, high-density, pre- $\beta$  subspecies of HDL, comprised predominantly of apolipoprotein (apo) A-I and phospholipid, is thought to act as the physiological acceptor for cholesterol in the extracellular matrix of peripheral tissues.<sup>11</sup> Peripheral availability of this "scavenger" particle appears to be regulated by the rates of synthesis, secretion, and catabolism of HDL.<sup>10-12</sup>

Both clinical and experimental data suggest that the principal protein constituent of HDL, apo A-I, mediates the antiatherogenic activity of HDL<sup>1</sup> and that the rate of production of apo A-I is a critical determinant of circulating HDL cholesterol. Families with both heritably deficient<sup>13-16</sup> and enhanced<sup>17</sup> apo A-I levels have been identified and show corresponding alterations in HDL cholesterol. Persons with familial hyperalphalipoproteinemia appear protected from atherosclerosis, while those deficient in apo A-I show accelerated cardiovascular disease. Mice transgenic for a copy of the human apo A-I gene demonstrate accumulation of human apo A-I in serum, increased circulating HDL cholesterol, and resistance to the atherogenic effects of a high cholesterol diet.<sup>18-21</sup> Thus, while the mechanisms regulating the rate of apo A-I synthesis are not clearly defined, genetic factors appear to exert an important effect.<sup>22</sup>

Received January 12, 1994; accepted May 10, 1994.

From the Departments of Internal Medicine (W.P.K., M.W., T.B., J.E.W., R.D.G., R.S.M.) and Biochemistry (R.D.G.), University of Texas Southwestern Medical Center, Dallas, Tex.

Presented in part at the Annual Meeting of the American Federation for Clinical Research, Washington, DC, April 30 to May 3, 1993, and published in abstract form (*Clin Res*. 1993;41:211A).

Correspondence to Robert S. Meidell, MD, Division of Cardiology, Molecular Cardiology Research Laboratories, NB11.106a, University of Texas Southwestern Medical Center, 6000 Harry Hines Blvd, Dallas, TX 75235-8573.

© 1994 American Heart Association, Inc.

STAFF LIBRARY  
PRESBYTERIAN-UNIVERSITY HOSPITAL



PATENT APPLICATION  
Serial No. 09/806,178  
Atty. Docket No. 702-010411

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit Not Yet Assigned :  
In re application of : **USE OF COMPOUNDS THAT REDUCE**  
**ALPHA2-ANTIPLASMIN IN VIVO FOR**  
Nobuo NAGAI et al. : **THE PREPARATION OF COMPOSITION**  
Serial No. 09/806,178 : **FOR THE TREATMENT OF ISCHEMIC**  
Filed June 18, 2001 : **STROKE**  
Examiner – Not Yet Assigned :

Pittsburgh, Pennsylvania  
August 29, 2001

**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Pursuant to the requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98, Applicants submit this Information Disclosure Statement which includes a completed Form PTO –1449. The references identified in Form PTO-1449 were cited in the International Search Report for the underlying PCT Application No. PCT/EP99/07405 or in the specification. Copies of the International Search Report and references cited in the specification are enclosed. Copies of the references cited in the International Search Report are not enclosed because the Notification of Acceptance of Application Under 35 U.S.C. § 371 and 37 C.F.R. § 1.494 or

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner for Patents, Washington, D.C. 20231 on August 29, 2001.

Barbara E. Johnson, Registration No. 31,198  
(Name of Registered Representative)

Signature

8/29/2001  
Date

2001 8 29 2001

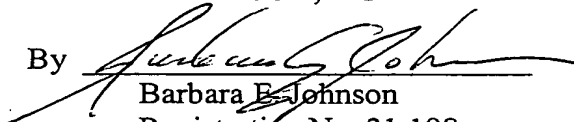
1.495 indicates that the International Search Report and the references cited therein were received by the USPTO.

Pursuant to 37 C.F.R. § 1.97(b)(2), no fee is believed to be due for the submission of this Information Disclosure Statement, as it is being submitted within three months of the date of entry of the national stage in an international application. Nevertheless, the Commissioner for Patents is hereby authorized to charge any fees which may be required to Deposit Account No. 23-0650. One original and two copies of this Information Disclosure Statement are enclosed.

Respectfully Submitted,

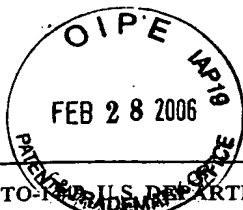
WEBB ZIESENHEIM LOGSDON  
ORKIN & HANSON, P.C.

By



Barbara E. Johnson  
Registration No. 31,198  
Attorney for Applicants  
700 Koppers Building  
436 Seventh Avenue  
Pittsburgh, PA 15219-1818  
Telephone: (412) 471-8815  
Facsimile: (412) 471-4094

MAO 8 2006

FORM PTO-100, U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEATTY. DOCKET NO.  
702-010411SERIAL NO.  
09/806,178INFORMATION DISCLOSURE STATEMENT  
STATEMENT BY APPLICANT

APPLICANT

Nobuo NAGAI et al.

(Use several sheets if necessary)

FILING DATE  
June 18, 2001GROUP  
ART UNIT Not Yet Assigned

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AL							
	AM							
	AN							
	AO							
	AP							

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	BR	Kopfler, W.P. et al. "Adenovirus-mediated transfer of a gene encoding human apolipoprotein A-I into normal mice increases circulating high-density lipoprotein cholesterol," <i>Circulation</i> 90(3): 1319-1327 (1994)
	BS	Carmeliet, P. et al. "Adenovirus-mediated transfer of tissue-type plasminogen activator augments thrombolysis in tissue-type plasminogen activator-deficient and plasminogen activator inhibitor-1-overexpressing mice," <i>Blood</i> 90(4): 1527-1534 (1997)
	BT	Carmeliet, P. et al. "Inhibitory role of plasminogen activator inhibitor-1 in arterial wound healing and neointima formation," <i>Circulation</i> 96(9): 3180-3191 (1997)

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

MAR 8 2006

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail

Mail Stop ISSUE FEE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
or Fax (703) 746-4000

FEB 28 2006

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below as indicated otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

28289

7590

10/25/2004

WEBB ZIESENHEIM LOGSDON ORKIN & HANSON, P.C.  
700 KOPPERS BUILDING  
436 SEVENTH AVENUE  
PITTSBURGH, PA 15219

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

## Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

Kimberly N. Welday	(Depositor's name)
<i>Kimberly N. Welday</i>	(Signature)
January 21, 2005	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,178	06/18/2001	Nobuo Nagai	702-010411	5455

TITLE OF INVENTION: USE OF COMPOUNDS THAT REDUCE ALPHA2-ANTIPLASMIN IN VIVO FOR THE PREPARATION OF A COMPOSITION FOR THE TREATMENT OF ISCHEMIC STROKE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	<del>\$1,370</del> \$1,400.00	\$0	<del>\$1,370</del> \$1,400.00	01/25/2005
EXAMINER	ART UNIT	CLASS-SUBCLASS			
NICHOLS, CHRISTOPHER J	1647	514-002000			

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

- (1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
- (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

WEBB ZIESENHEIM  
LOGSDON ORKIN &  
HANSON, P.C.

## 3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

Desire Jose Collen

and Leuven Research &amp; DevelopmentVZQ

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

BELGIUM

BELGIUM

Please check the appropriate assignee category or categories (will not be printed on the patent): ☒ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):

- ☒ A check in the amount of the fee(s) is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number \_\_\_\_\_ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above. NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature

Barbara E. Johnson

Date January 21, 2005

Registration No. 31,198

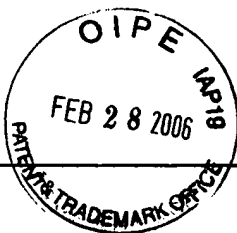
This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.





UNITED STATES  
PATENT AND  
TRADEMARK OFFICE



AUGUST 28, 2003

PTAS

WEBB ZIESENHEIM LOGSDON & ET AL.  
BARBARA E. JOHNSON  
436 7TH AVENUE  
700 KOPPERS BUILDING  
PITTSBURGH, PA 15219-1818

Deputy Under Secretary of Commerce For Intellectual Property and  
Deputy Director of the United States Patent and Trademark Office  
Washington, DC 20231  
www.uspto.gov



\*102410984A\*

UNITED STATES PATENT AND TRADEMARK OFFICE  
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 04/01/2003

REEL/FRAME: 013912/0343  
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

LEUVEN RESEARCH & DEVELOPMENT VZW

DOC DATE: 03/10/2003

ASSIGNEE:

COLLEN, DESIRE JOSE  
SCHOONZICHTLAAN 20  
WINKSELE-HERENT, BELGIUM B-3020

ASSIGNEE:

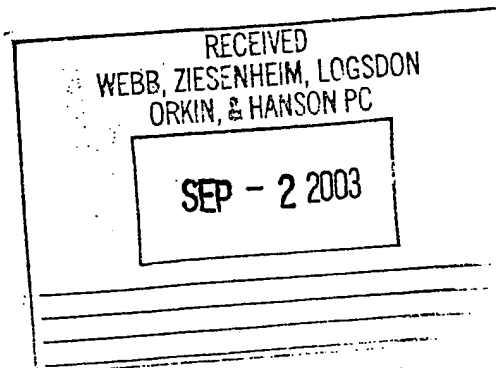
LEUVEN RESEARCH & DEVELOPMENT VZW  
BENEDENSTRAAT 59A  
LEUVEN B-3000, BELGIUM

SERIAL NUMBER: 09806178

PATENT NUMBER:

FILING DATE: 06/18/2001

ISSUE DATE:



C-VE-51-2

## ASSIGNMENT

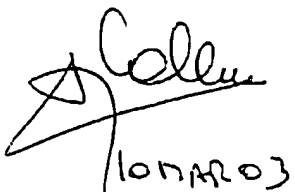
WHEREAS, LEUVEN RESEARCH & DEVELOPMENT VZW, a corporation organized under the Laws of Belgium, doing business and having their post office address at Benedenstraat 59A, B-3000 Leuven, Belgium (hereinafter called "Assignor") is the sole and exclusive assignor of the United States Patent Application Serial No. 09/806,178, filed June 18, 2001, entitled "Use of Compounds that Reduce Alpha2-Antiplasmin In Vivo for the Preparation of Ischemic Stroke"; and

WHEREAS, Desiré José Collen, an individual, whose post-office address is Schoonzichtlaan 20, B-3020 Winksele-Herent, Belgium, and LEUVEN RESEARCH & DEVELOPMENT VZW (hereinafter "Co-Assignees"), are desirous of acquiring joint right, title, and interest in and to said United States Patent Application and the inventions covered thereby.

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00) U.S. and other good and valuable consideration, the receipt of which is hereby acknowledged, Assignor has sold, assigned, transferred and set over, and does hereby sell, assign, transfer and set over to Co-Assignees respective undivided interests in United States Patent Application Serial No. 09/806,178, and any continuations, continuations-in-part, divisionals, and reissues thereof, and the inventions covered thereby, the same to held and enjoyed by Co-Assignees for their own use and enjoyment, and for the use and enjoyment of their successors, assigns or other legal representatives, to the end of the term for which a patent is granted or reissued as fully and entirely as the same would have been held and enjoyed by Assignor, if this assignment and sale had not been made; together with all claims for damages by reason of past infringement of said patent, with the right to sue for and collect the same for their own use and enjoyment, and for use and enjoyment of their successors, assigns and other legal representatives.

ASSIGNOR hereby authorizes and requests the United States Commissioner of Patents and Trademarks to record this assignment to Co-Assignees of the entire interest, and hereby covenants that it has full right to convey the entire interest herein assigned, and that it has not executed, and will not execute, any agreements inconsistent therewith.

IN WITNESS WHEREOF, Assignor has caused this assignment to be executed effective this 10 day of March, 2003

  
LEUVEN RESEARCH & DEVELOPMENT VZW

By

R DE BOND

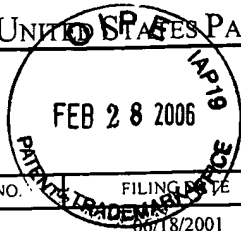
Title

CHAIRPERSON

MAR 8 2003



# UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,178	06/18/2001	Nobuo Nagai	702-010411	5455

Russell D Orkin  
700 Koppers Building  
436 Seventh Avenue  
Pittsburg, PA 15219-1818

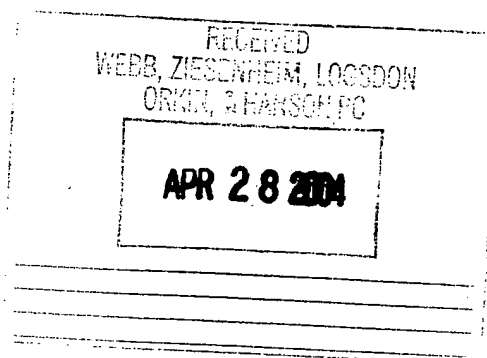
7590

04/26/2004

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.



**Office Action Summary**

Application No.

09/806,178

Applicant(s)

NAGAI ET AL.

Examiner

Christopher J Nichols, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 7 and 12-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7 and 12-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 7 and 12-14 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

MAR 8 2006

**Notice of References Cited**

Application/Control No.

09/806,178

Applicant(s)/Patent Under  
Reexamination  
NAGAI ET AL.

Examiner

Christopher J Nichols, Ph.D.

Art Unit

1647

Page 1 of 2

**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

**FOREIGN PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

**NON-PATENT DOCUMENTS**

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research 10:398-400
	V	Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in th genomic era." Trends in Biotech. 18(1): 34-39
	W	Doerks et al., (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics 14(6): 248-250
	X	Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology 15:1222-1223

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,178	06/18/2001	Nobuo Nagai	702-010411	5455

7590 05/05/2003

Russell D Orkin  
700 Koppers Building  
436 Seventh Avenue  
Pittsburg, PA 15219-1818

EXAMINER

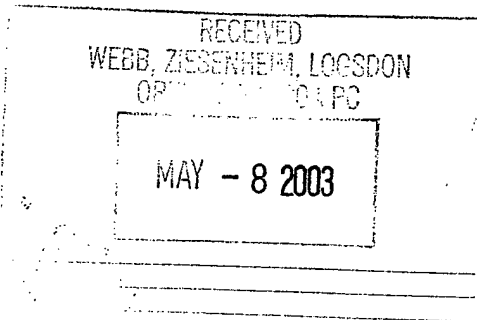
NICHOLS, CHRISTOPHER J

ART UNIT PAPER NUMBER

1647

DATE MAILED: 05/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.



1003 8 2006

**Office Action Summary**

Application No.

09/806,178

Applicant(s)

NAGAI ET AL.

Examiner

Christopher Nichols, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 7 and 12-15 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7 and 12-15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121. . . . 2005

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 8
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152) 2005
- 6) ☐ Other:

<b>Notice of References Cited</b>	Application/Control No. 09/806,178	Applicant(s)/Patent Under Reexamination NAGAI ET AL.	
	Examiner Christopher Nichols, Ph.D.	Art Unit 1647	Page 1 of 2

**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

**FOREIGN PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

**NON-PATENT DOCUMENTS**

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Lapchak et al. (September 2002) "Microplasmin: A Novel Thrombolytic That Improves Behavioral Outcome After Embolic Strokes in Rabbits." Stroke 33(9): 2279-2284.
	V	Bell (1997) "Evaluation of Thrombolytic Agents." Drugs 54(Supplement 3): 11-17.
	W	Smalling (15 November 1997) "A fresh look at the molecular pharmacology of plasminogen activators: From theory to test tube to clinical outcomes." Am. J. Health-Syst. Pharm. 54(Suppl. 1): S17-S22.
	X	Nagai et al. (15 May 2001) "Depletion of circulating a2-antiplasmin by intravenous plasmin or immunoneutraliz6oin reduce focal cerebral ischemic injury in the absence of arterial recanalization." Blood 97(10): 3086-3092.

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.